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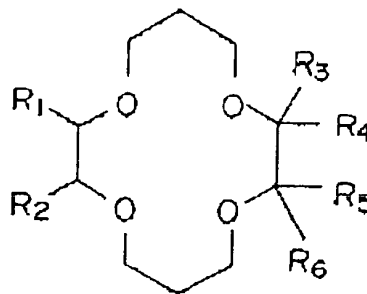
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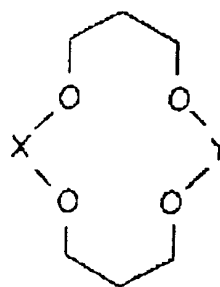
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TITLE : ION SELECTIVE COORDINATION
MOLECULE AND ION SENSOR



I



II

ABSTRACT : PURPOSE: To provide a new compound useful as a highly selective ion sensor (ion electrode) in the field of industrial process, food, basic medical research, etc.

CONSTITUTION: The compound of formula I (R₁ to R₆ are H or hydrocarbon group; at least one of R₁ to R₆ is hydrocarbon group). The compound of formula I can be produced from a compound of formula II.

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Specification

(54) Title of the Invention: Ion Selective Coordination Molecules and Ion Sensors

(57) Abstract

Objective: Ion-Selective Coordination Molecules with Extremely High Selectivity

Configuration: The ion-selective coordination molecule represented by the general formula (i), below.

[Chemical Formula 1]

/formula/

(i)

Where R1 ~ R6 in the formula (i) are each an independent hydrogen or hydrocarbon group and at least one of the elements R1 ~ R6 is a hydrocarbon group.

Effect: The highly selective ion sensors (ion electrodes) made using the molecules of this invention are extremely useful, and can be used in a wide variety of fields, including industrial processes, foods and basic medical research.

Scope of Patent Claims

Claim 1

The ion-selective coordination molecule represented by the following general formula (i).

Formula 1

/formula/ (i)

Where R1 ~ R6 in the formula (i) are each an independent hydrogen or hydrocarbon group and at least one of the elements R1 ~ R6 is a hydrocarbon group.

Claim 2

The ion-selective coordination molecule represented by the following general formula (ii).

Formula 1

/formula/ (ii)

Where R7 ~ R9 in the formula (ii) are each an independent hydrogen or hydrocarbon group and at least one of the elements R7 ~ R9 is a hydrocarbon group.

Claim 3

The ion-selective coordination molecule represented by the following general formula (iii).

Formula 3

/formula/ (iii)

Where R10 ~ R13 in the formula (iii) are each an independent hydrogen or hydrocarbon group and at least one of the elements R10 ~ R13 is a hydrocarbon group.

Claim 4

The ion-selective coordination molecule represented by the following general formula (iv).

Formula 4

/formula/ (iv)

Where R14 ~ R17 in the formula (iv) are each an independent hydrogen or hydrocarbon group and at least one of the elements R14 ~ R17 is a hydrocarbon group.

Claim 5

An ion sensor that uses any of the ion-selective coordination molecules described in Claims 1 ~ 4 as a sensing material.

Detailed Description of the Invention

0001

Industrial Fields of the Invention

This invention pertains to the sensing materials used in ion sensors (ion electrodes). In particular, it pertains to ion-selective coordination molecules that are suitable for use as the sensing material in ion sensors and are highly selective with respect to lithium ions, magnesium ions and calcium ions. It also pertains to ion sensors that use ion-selective coordination molecules.

0002

Prior Art

There are known techniques for using chemical compounds such as valimycin and other ring peptides, benzo [15] crown-5 and other ring polyethers, nonactin, monactin, dinactin, trinactin, tetranactin and other nactins. (See JSP S59-163557.) By using chemical compounds of this sort as sensing materials, this technology makes it possible to detect with a high degree of

accuracy, positive ions such as ammonium ions, sodium ions and potassium ions that were previously considered impossible to detect. As a group, chemical compounds of this sort are known as ion-selective coordination molecules (or neutral ionophores, an ion-sensing substance). Of the ion-selective coordination molecules there have been reports regarding lithium ions in which 14 crown 4 inductors were used in lithium ion sensors (Keiichi Kimura et al, Analytical Chemistry, Vol. 59, pp. 2331 ~ 2334, 1987 (Citation (1))). Concerning magnesium ions and calcium ions there was a report by Wilhelm Simon, for example in Analytical Chemistry, Vol. 61, pp. 574 ~ 576, 1989 (Citation (2)) and Vol. 58 of the same periodical, pp.2282 ~ 2285, 1986 (Citation (3)).

0003

Problems the Invention Attempts to Solve

However, no matter what the application was, it was always desired that the performance of the ion sensors be selective. Ion-selective coordination molecules with even greater selectivity were eagerly sought. This invention was developed with the above in mind, and it provides ion-selective coordination molecules that have extremely high selectivity as well as ion sensors that use those ion-selective coordination molecules as sensing materials.

0004

Means for Solving Problems

The invention described in claim 1 is the ion-selective coordination molecule represented by the following general formula (i).

/formula/ (i)

Where R1 ~ R6 in the formula (i) are each an independent hydrogen or hydrocarbon group and at least one of the elements R1 ~ R6 is a hydrocarbon group.

0005

The invention described in Claim 2 is the ion-selective coordination molecule represented by the general formula (ii) below.

[Formula 6]

/formula/ (ii)

Where R7 ~ R9 in the formula (ii) are each an independent hydrogen or hydrocarbon group and at least one of the elements R7 ~ R9 is a hydrocarbon group.

0006

The invention described in Claim 3 is the ion-selective coordination molecule represented by the general formula (iii) below.

[Formula 7]

/formula/ (iii)

Where R10 ~ R13 in the formula (iii) are each an independent hydrogen or hydrocarbon group and at least one of the elements R10 ~ R13 is a hydrocarbon group.

0007

The invention described in Claim 4 is the ion-selective coordination molecule represented by the general formula (iv) below.

[Formula 8]

/formula/ (iv)

Where R14 ~ R17 in the formula (iv) are each an independent hydrogen or hydrocarbon group and at least one of the elements R14 ~ R17 is a hydrocarbon group.

0008

The ion sensor of this invention uses the ion-selective coordination molecules described in any of Claims 1 through 4 as a sensing material.

0009

Embodiments

Embodiment 1

We synthesized the chemical compounds that are new substances and are represented by formulae (i) and (ii) as sensing materials that are extremely selective in relation to lithium ions.

0010

[Formula 9]

/formula/ (i)

Where R1 ~ R6 in the formula (i) are each an independent hydrogen or hydrocarbon group and at least one of the elements R1 ~ R6 is a hydrocarbon group.

0011

[Formula 10]

/formula/ (ii)

Where R7 ~ R9 in the formula (ii) are each an independent hydrogen or hydrocarbon group and at least one of the elements R7 ~ R9 is a hydrocarbon group.

0012

These new lithium ion-selective coordination molecules (i) and (ii) are based on the model molecule concept represented by the model molecular formula (a) below.

0013

[Formula 11]

/formula/ (a)

0014

The basic framework of the model molecular formula (a) is based on the 14 crown 4 which is known to have holes with diameters that correspond to the size of lithium ions. Tall side chains or subunits have been introduced in the X and Y positions in the model molecular formula (a). Using this structure means that ions with a diameter larger than that of lithium ions are blocked by the side chains (subunits) in the X and Y positions so that stable ion coordination chemical compounds are not formed. A tall subunit such as 2,2,3,3-tetramethyl, pinan or decolino groups would be suitable in the X or Y positions. However, that doesn't necessarily

mean that introducing 2 tall groups into the X and Y positions will improve lithium selectivity. The reason is that the lithium ions themselves would be blocked by the 2 tall groups, making ion coordination difficult. For this reason, it is better to have a tall element in the X or the Y position and one that is not tall in the other position. In the chemical compound represented by Formula (i), R1 through R6 are each an independent hydrogen or hydrocarbon group and it is preferred that at least one of R1 through R6 be a hydrocarbon group. In the chemical compound represented by Formula (ii), R7 through R9 are each an independent hydrogen or hydrocarbon group and it is preferred that at least one of R7 through R9 be a hydrocarbon group. In particular, when these chemical compounds are used in ion sensors they add durability so it is desirable that an alkyl group, (especially a long chain alkyl group), a benzyl group (especially a benzyl oxymethyl group) a phenyl group or cyclohexyl group be introduced to at least 1 of the basic ring side chains; that is, to at least 1 of the hydrocarbon groups R1 through R9.

0015

In the chemical compounds shown in the chemical formula (i), a molecule in which benzyl oxymethyl groups have been introduced to R1 and R2 and methyl groups have been introduced to R3, R4, R5 and R6 are shown in the chemical formula (b) below. Note that according to the IUPAC naming conventions this molecule is called trans-2,3-dibenzylloxymethyl-9, 9, 10, 10-tetramethyl-1, 4, 8, 11-tetraoxacyclotetradecane.

[Formula 12]

/formula/

(b)

0016

Additionally, the chemical formula (c) below shows an example of the chemical compound shown in Chemical Formula (ii), where H has been introduced into R7, an long-chain alkyl group has been introduced into R8 and a methyl group has been introduced into R9. Note also that according to the IUPAC naming conventions this molecule is called Tricyclo [12,4,1^{2,4},0^{1*6}] – 1,3,3-trimethyl-12-tetradecyl-7,11,14,18-tetraoxacyclononadecane.

[Formula 13]

/formula/

(c)

0017

When we made ion sensors using these ion-selective coordination molecules as the sensing material, we were able to create lithium ion sensors (lithium ion-selective electrodes) that have 1000 times more sensitivity to all alkali metal ions and alkali earth metal ions in addition to lithium ions.

0018

We show an example of the synthesis of the chemical compound (b) below. First, (2.54 grams, 1.06 mmol, 2.5 eq) of sodium hydride was gradually added to (5.00 grams, 42.3 mmol) of a pinacol (chemical compound (1) below) anhydrous tetrahydrofuran (THF) solution while stirring. Next 25 ml of a (12.8 grams, 106 mmol, 2.5 eq) allyl bromide, anhydrous THF solution was dripped for 50 minutes and then stirred for an additional 15 hours at 80° C. Methanol was added and after the reaction was finished it was concentrated. This was separated and extracted using an ethyl acetate water system. The ethyl acetate layer was washed three times using water. Next, the first water layer was reverse-extracted once using ethyl acetate. Then all of the acetic

acid layers were dried with sodium sulfate and concentrated. This was separated and purified using silica gel column chromatography (eluent: hexane/ethyl acetate : 4/1) yielding the chemical compound (2) below. (3.92 g, recovery rate of 46.7 %)

[Formula 14]

/formula/

0019

0.673 g (17.8 mmol, 0.9 eq) of finely ground sodium boron hydride was added to 60 ml of an anhydrous THF solution containing 3.92 g (19.8 mmol) of the chemical compound produced above (2). Over a one hour period, 20 ml of an anhydrous THF solution containing 3.36 g (23.7 mmol, 1.2 eq) of boron trifluoride etherate was dripped while stirring, after which, the stirring was continued for 13 more hours. Next, water was added and the excess sodium boron hydride was crushed. An aqueous solution of 0.569 g (14.2 mmol, 0.72 eq) of 3N sodium hydroxide was added and then 30 % hydrogen peroxide water (9.6 ml) was added slowly. After stirring for three hours the reaction was finished and concentrated. This was separated and extracted using an ethyl acetate water system. The ethyl acetate layer was washed three times with water. The first and second layers of water were reverse-extracted together using ethyl acetate. After reverse-extracting all of the ethyl acetate layers using ethyl acetate, we dried and then concentrated all of the ethyl acetate layers using sodium boron hydride. The concentrated residue was separated and purified using silica gel column chromatography (eluent: hexane/ethyl acetate : 1/5) yielding the diol chemical compound (3) below. (2.06 g, recovery rate of 44.5 %).

[Formula 15]

/formula/

0020

We added anhydrous pyridine to 2.03 g (8.79 mmol) of the chemical compound (3) obtained above. Then we stirred it for 30 minutes in an ice bath. Next we added 4.19 g (22.0 mmol, 2.5 eq) p-toluenesulfonyl chloride and stirred for five hours in an ice bath. After the reaction was finished we added toluene to remove the pyridine and concentrated it. This was separated using a chloroform-water system and the chloroform layer was washed three times with water. After drying the chloroform layer with sodium sulfate, we concentrated it. The concentrated residue was separated and purified using silica gel column chromatography (eluent: hexane/ethyl acetate: 3/1). This produced the ditosilate chemical compound (4) below. (1.22 g, recovery rate: 25.6 %)

[Formula 16]

/formula/

0021

We slowly added 31.8 mg (1.33 mmol, 2.4 eq) of sodium hydroxide to 30 ml of an anhydrous THF solution containing 167.1 mg (0.55 mmol) of threitol ((+) – 1, 4-di-o-benzyl-D-threitol, the chemical compound (5) below) and stirred it for 1 hour. To this we added the anhydrous THF solution containing 300 mg (0.55 mmol, 1 eq) of the ditosilate (chemical compound (4)) produced above and stirred it for 96 hours at 70 ° C and then for 87 hours at 90 ° C. After we added methanol and finished the reaction, we concentrated it and separated and extracted the liquid using a chloroform system. We washed the chloroform layer 4 times with water. After washing the chloroform layer with boron sodium hydride we concentrated it. The

concentrated residue was separated using silica gel column chromatography (eluent: hexane/ethyl acetate: 4/1). This was separated and purified using high-performance liquid chromatography (HPLC) (eluent: methanol) yielding the chemical compound (6) below (37.4 mg, recovery rate of 13.5 %)

[Formula 17]

/formula/

0022

The chemical compound (6) was a colorless viscous liquid. When we ran an elemental analysis on this, the calculated values for the chemical compound (b) were C: 72.0 %, H: 8.9 %, O: 19.1 %. In contrast, the actual measured values of the chemical compound (6) were C: 71.8 %, H: 9.0%, O: 19.2%. The results of this elemental analysis also verified that the product of the reaction (6) that we obtained was the target chemical compound (b).

0023

We show an example of the synthesis of chemical compound (c) below. First, 2 g (7.7 mmol) of the chemical compound (10) below was dissolved in 15 ml of dimethyl formamide. We added 2.4 times that volume of allyl bromide (2.3 g, 18.6 mmol) and then slowly added 3 times (0.56, 23.2 mmol) the volume of sodium hydroxide in an ice bath. Gradually the temperature was raised to 80 ° C and stirred for three days, producing the chemical compound (11) below at a 40 % recovery rate.

0024

[Formula 18]

/formula/

0025

We placed 3.4 g (10 mmol) of the chemical compound (11) described above in 30 ml of an anhydrous THF solution and then added 0.34 g (9 mmol, 0.9 eq) of finely ground sodium boron hydride. While stirring at room temperature, we then dripped 10 ml of an anhydrous THF solution of 1.7 g (12 mmol, 1.2 eq) of boron trifluoride etherate over a 1- hour period. We stirred this for an additional 13 hours. We added water to break down the excess sodium boron hydride and added an aqueous solution with 0.29 g of 3N sodium hydroxide (7 mmol, 0.72 eq). Next, we slowly added 5 ml of 30% hydrogen peroxide water. After 3 hours of stirring, we stopped the reaction and concentrated it. This was separated and extracted using an ethyl acetate system and the ethyl acetate layer was washed 3 times with water. The first and second water layers were reverse-extracted once using ethyl acetate and concentrated, after drying all of the ethyl acetate layers using sodium sulfate. The concentrated residue was separated and purified using silica gel chromatography (eluent: hexane/ethyl acetate : 1/5), yielding 2.0 g (recovery rate of 55%) of the diol shown in the chemical compound (12) below.

0026

[Formula 19]

/formula/

0027

2.0 g (5.4 mmol) of the chemical compound (12) described above was added to anhydrous pyridine. Then it was stirred in an ice bath for 30 minutes. Next, we added 2.6 g (13.5 mmol, 2.5 eq) of p-toluenesulfonyl chloride and stirred it in an ice bath for 5 hours. After the reaction was finished, we added toluene to remove the pyridine and concentrated it. This was separated using a chloroform-water system and the chloroform layer was washed three times with water. After drying the chloroform layer with sodium boron hydride we concentrated it. The concentrated residue was separated and purified using silica gel column chromatography (eluent: hexane/ethyl acetate: 1/5). This produced the ditosilate chemical compound (13) below. (1.84 g, recovery rate of 50%)

0028

[Formula 20]

/formula/

0029

We added 0.23 mg (11 mmol, 4 eq) of sodium hydride, to 20 ml of anhydrous dimethylformamide (DMF) solution with 0.46 g (2.7 mmol) of pinanediol (the chemical compound (14) shown below), at room temperature while stirring. We continued stirring for an hour. We added 20 ml of an anhydrous DMF solution containing 1.84 g (2.7 mmol, 1 eq) of the ditosilate chemical compound (13) produced above and stirred for 60 hours at 90 °C. We then added methanol and finished the reaction. After concentrating it, it was separated and extracted using a chloroform water system. After that, we dried the chloroform layer using sodium sulfate and concentrated it. The concentrated residue was separated using silica gel column chromatography (eluent: hexane/ethyl acetate : 15/1) and then high-performance liquid chromatography was used in separation and purification, (solvent separation solution: methanol), yielding 69 mg of the chemical compound (15) shown below. (Recovery rate of 5%). This is how the chemical compound (c) was synthesized.

0030

[Formula 21]

/formula/

0031

Embodiment 2

We synthesized new substances as sensing materials, which are extremely selective to magnesium ions and calcium ions, that are expressed in the chemical compounds shown in the chemical formulae (iii) and (iv) below.

0032

[Formula 22]

/formula/

Where R10 ~ R13 in the formula (iii) are each an independent hydrogen or hydrocarbon group and at least one of the elements R10 ~ R13 is a hydrocarbon group.

0033

[Formula 23]

/formula/

Where R14 ~ R17 in the formula (iv) are each an independent hydrogen or hydrocarbon group and at least one of the elements R14 ~ R17 is a hydrocarbon group.

0034

These new magnesium ion-selective coordination molecules and calcium ion-selective coordination molecules are based on a model molecule similar to the one shown by the model molecule (d) below.

0035

[Formula 24]

/formula/

0036

The model molecule (d) uses a ring-shaped azacrown for its basic framework and it is easier for the positive ions to orient to the holes of rings with a high electron density such as oxygen atoms or nitrogen atoms. However, that by itself would not be sufficient to cause coordination toward alkali earth metal ions such as magnesium or calcium; so a side chain that has amide bonding at the Z-position is introduced, which strengthens the coordination force for these ions. When we studied the Z-section side chains, we learned that the malonamide type (chemical formula (e) below) was particularly well-suited to this.

0037

[Formula 25]

/formula/

0038

And, that the diglycolic amide type (chemical formula (f) below) was particularly well-suited to calcium ions.

0039

[Formula 26]

/formula/

0040

These are units that exist in the magnesium and calcium ion-selective coordination molecules in Citations (2) and (3) above, which were published previously by Wilhem Simon et al. However, the ion-selective performance of said ion-selective coordination molecules was not sufficient. The ion-selective coordination molecules of this invention, which have azacrown rings as a necessary structural framework, could have far superior ion-selective performance. The azacrown ring is the basic ring and, for magnesium ions, an 18-member ring is suitable, while for the calcium ion, a 21-member ring is better. Additionally, in the chemical formulae (iii) and (iv), the terminals in the side chains, which are R10 ~ R13 and R14 ~ R17, are hydrogen or hydrocarbon groups and at least one of those from R10 ~ R13 and R 14 ~ R17 is an alkyl group

(especially a normal alkyl group). Or, it would be preferred that tall groups, like the adamantyl group (the chemical formula (g) below) or the cyclohexyl group be highly selective.

[Formula 27]

/formula/

0041

The chemical compound (h) below shows the chemical compound (iii), where magnesium ion-selective adamantyl groups have been introduced into R10 and R12 and hydrogen has been introduced into R11 and R13. Note that according to the IUPAC naming conventions the chemical compound (h) would be 4, 13-di-N-adamantanecarbamoylacetyl-1, 7, 10, 16-tetraoxa-4, 13 – diazacyclooctadecane.

0042

[Formula 28]

/formula/

0043

A magnesium ion-selective coordination molecule where alkyl groups were introduced in R10 and R12 and hydrogen was introduced into R11 and R13 is shown in the chemical compound (k) below. Note that according to the IUPAC naming conventions, the chemical compound (k) would be called 4, 13-di-N-dodecyl carbamoylacetyl – 1, 7,10, 16-tetraoxa-4, 13-diazacyclooctandecane.

0044

[Formula 29]

/formula/

0045

A calcium ion-selective coordination molecule, where adamantyl groups have been introduced into R14 and R16 and hydrogen has been introduced into R15 and R17 is shown in the chemical compound (l) below. Note that according to the IUPAC naming conventions, the chemical compound (l) would be called 4, 13-di-N-1-adamantanecarbamoyl – 3 – oxabutyryl-1, 7, 10, 13, 19 – pentaoxa-4, 16-diazacyclohenicosane.

0046

[Formula 30]

/formula/

0047

A calcium ion-selective coordination molecule, where alkyl groups have been introduced into R14 and R16 and hydrogen has been introduced into R15 and R17 is shown in the chemical compound (m) below. Note that according to the IUPAC naming conventions, the chemical compound (m) would be called 4, 16-di-N-dodecyl carbamoyl -3- oxabutyryl-1, 7-10, 13, 19 – pentaoxa-4, 16-diazacyclohenicosane.

0048

[Formula 31]

/formula/

0049

When we made ion sensors (ion-selective electrodes) using the above ion-selective coordination molecules we were able to produce sensors that had a much higher degree of selectivity than magnesium ion or calcium ion selective electrodes reported to date.

0050

We show an example of the synthesis of the above ion-selective coordination molecule (h) below. We synthesized the side chain section of the synthesized substance (h). We synthesized (the method of synthesis has been omitted) malonic acid monomethyl ester chloride, the chemical compound (17) below, from 3 g (19.2 mmol) of malonic acid mono methyl ester potassium salt, the chemical compound (16) below. Next, we added the malonic acid monomethyl ester chloride to 20 ml of an anhydrous methylene chloride solution, into which 500 g (3.3 mmol) of 1-adamantanamine (the chemical compound (18) below, where Ada is an adamantyl group) had been added. This was stirred for 24 hours in an ice bath. After the reaction was finished, separation and extraction of the reaction system were carried out using chloroform and hydrochloric acid with a pH of 2. The chloroform layer was washed once with water and, after drying it with sodium sulfate, it was concentrated. It was recrystallized with methanol and water, producing 640 mg (recovery rate of 77.0%) of the yellowish-white crystal malonic acid methylester N-1-adamantylamido (chemical compound (19) below). Note: this chemical compound (19) was measured using NMR. $^1\text{H-NMR}$: $\delta = 1.62 \sim 1.75$ (m, 6H, H-6), $1.95 \sim 2.13$ (m, 9H, H-4, H-5), 3.23 (s, 2H, H-2), 3.74 (s, 3H, H-1), $6.65 \sim 6.80$ (br, 1H, H-3).

0051

[Formula 32]

/formula/

0052

We added 640 mg (2.55 mmol) of the chemical compound (19) obtained above to a mixed solution containing 10 ml of methanol and 5 ml of water. Then we added 210 mg (5.1 mmol) of lithium hydroxide and stirred it for 15 hours at room temperature. After the reaction was finished, the reaction system was concentrated and dissolved in water until the pH was around 2. Then we performed 3 reverse-extractions with chloroform. The chloroform layer was washed with water and after drying it with sodium sulfate, it was concentrated, yielding 383 mg (recovery rate of 63.6%) of malonic acid N-1-adamantylamido, the chemical compound (20) below, which is a yellowish-white crystal that is a side chain. This chemical compound (20) was measured using NMR.

$^1\text{H-NMR}$: $\delta = 1.63 \sim 1.80$ (m, 6H, H-6), $1.96 \sim 2.17$ (m, 9H, H-4, H-5), 3.22 (s, 2H, H-2), $5.60 \sim 5.70$ (br, 1H, H-3).

0053

[Formula 33]

/formula/

0054

Next, we introduced the side chain produced above into the azacrown ring. 270 mg (1.14 mmol) of the chemical compound (20) obtained above was placed in 9 ml of anhydrous methylene chloride. We added 0.32 ml (2.29 mmol) of triethylamine while stirring. After 15 minutes, we added 291 mg (1.14 mmol) of BOP and then 15 minutes after that, we added 150 mg (0.57 mmol) of kryptofix (the chemical compound (21) below) and continued stirring for two days in an ice bath. After the reaction was complete, we concentrated the reaction system and ran two separation extractions using hydrochloric acid with a pH of 1. We washed the chloroform layer with water, dried it with sodium sulfate and concentrated it. Next, we used high-performance liquid chromatography (HPLC) (eluent: methanol) for 15 minutes to separate the layers, which yielded 320 mg (recovery rate of 80.0%) of the yellowish-white needle-shaped crystal chemical compound (22) that is shown below. This product (22) was measured using NMR.

$^1\text{H-NMR}$: $\delta = 1.60 \sim 1.80$ (m, 12H, H-8), $1.93 \sim 2.13$ (m, 18H, H-6, H-7), $3.20 \sim 3.30$ (m, 4H, H-4), $3.54 \sim 3.80$ (m, 24H, H-1 \sim 3), $7.25 \sim 7.30$ (br, 2H, H-4).

We also ran infrared spectroscopy.

IR (cm^{-1}): $\nu_{\text{as}}(\text{C-O}) = 1111.0$, $\delta_{\text{s}}(\text{CH}) = 1454.5$, $\delta_{\text{s}}(\text{NH}) = 1548.1$, $\nu_{\text{s}}(\text{C}=\text{O}) = 1634.8$, $\nu_{\text{s}}(\text{CH}_2) = 2851.0$, $\nu_{\text{as}}(\text{CH}_2) = 2907.5$, $\nu_{\text{as}}(\text{NH}) = 3313.4$

When we performed an elemental analysis, the calculated values were C: 65.1%, H: 8.63%, O: 18.3% while the actual measurements of the substance produced (22) were C: 65.3%, H: 8.7%, O: 18.1%. Thus, we were able to confirm that the product (22) was the chemical compound (h).

0055

[Formula 34]

0056

We show an example of the synthesis of the new chemical compound (k) below, where we synthesized the side chain section. We suspended 3.0 g (19.2 mmol) of malonic acid monomethyl ester potassium salt in 20 ml (6 times the volume) of an anhydrous methylene chloride solution. Then, we dripped thionyl chloride at 0 °C and stirred for 2 hours, which synthesized the malonic acid monomethyl ester chloride (the chemical compound (23) shown below). After that, we ran the potassium chloride reaction residue through a vacuum filter to concentrate it. We then added it to 20 ml of an anhydrous methylene chloride solution, to which 3.56 g (19.2 mmol) of lauryl amine (the chemical compound (24) shown below) had been added and stirred it for 3 hours at 0 °C. After the reaction was finished, we separated and extracted the reaction system using chloroform and hydrochloric acid with a pH of 2. After washing once with water, the chloroform layer was dried using sodium sulfate and concentrated. Recrystallization with methanol-water yielded 540 mg (recovery rate of 10%) of the yellowish-white crystal malonic acid methylester N-dodecylamide (the chemical compound (25) shown below). The chemical compound (25) was measured using NMR.

$^1\text{H-NMR}$ (ppm): $\delta = 0.83$ (t, 3H, H-15), 1.22 (m, 18H, H-6, H-14), 1.49 (t, 2H, H-5), 3.21 (q, 2H, H-4), 3.38 (s, 2H, H-2), 3.69 (s, 3H, H-1), $7.35 \sim 7.35 \sim 7.48$ (br, 1H, H-3).

0057

[Formula 35]

/formula/

0058

540 mg (1.89 mmol) of the chemical compound (25) produced above was added to a mixed solution containing 15 ml of methanol and 5 ml of water. We then added 0.16 g (3.78 mmol) of lithium hydroxide and stirred it for 15 hours. After we concentrated the reaction system, we dissolved it in water. When it reached a pH of around 2, we did 3 reverse-extractions using chloroform and washed it several times in water. After drying the chloroform layer in sodium sulfate, we concentrated it, which yielded 486 mg (recovery rate of 95%) of malonic acid N-dodecylamide (the chemical compound (26) below), which would become the side chain. We measured the chemical compound (26) using NMR.

$^1\text{H-NMR}$: δ = 0.87 (t, 2H, H-14), 1.27 (m, 18H, H-5 ~ 13), 1.53 (t, 2H, H-4), 3.22 (q, 4H, H-3), 6.88 ~ 7.00 (br, 1H, H-2).

0059

[Formula 36

/formula/

0060

Next, we introduced the side chain produced above, into the azacrown ring. We added 206.9 mg (0.76 mmol) of the chemical compound (26) obtained above to 7 ml of anhydrous methylene chloride and then, while stirring, added 0.32 ml (2.2 mmol) of triethylamine. 15 minutes later, we added 194 g (0.76 mmol) of BOP and 15 minutes after that, we added 100 mg (0.38 mmol) of kryptofix (chemical compound (21)). We continued stirring the mixture in an ice bath for 2 days. After the reaction was finished, we concentrated the reaction system and ran two separation extractions. We then washed the chloroform layer with water, dried it with sodium sulfate and concentrated it. Next, we used HPLC (eluent: methanol) to run a separation for 28 minutes, producing 128 mg (recovery rate of 43.7%) of the white crystal chemical compound (27) below. Note that all of the chemical compounds used as ionophores are desalinated using hydrochloric acid and washed using water. The substance produced (27) was measured using NMR.

$^1\text{H-NMR}$: δ = 0.88 (t, 6H, H-25, J = 6.95 Hz), 1.15 ~ 1.40 (m, 36H, H-16 ~ 24), 1.40 ~ 1.57 (m, 4H, H-15), 3.24 (q, 4H, H-14, J = 7.27 Hz), 3.34 (d, 4H, H-13), 3.50 ~ 3.75 (m, 24H, H1 ~ 12), 7.63 ~ 7.77 (br, 2H, H-A).

Measurements were made using infrared spectrometry.

IR (cm^{-1}) : ν_{as} (C-O) = 1116.5, δ_{s} (NH) = 1567.5, ν_{s} (C = O) = 1639.5, ν_{s} (CH₂) = 2849, ν_{as} (CH₂) = 2917.2, ν_{s} (NH) = 3273.9

When we performed an elemental analysis, the calculated values for the chemical compound (k) were C: 65.59%, H: 10.48%, N: 7.28%, while the actual measurements of the substance produced (27) were C: 65.54%, H: 10.22%, N: 7.19%. Thus, we were able to confirm that the product (27) was the chemical compound (k).

0061

[Formula 37]

/formula/

0062

The following is an example of synthesizing chemical compound 91). The section that was to be the side chain was prepared using the following method. 1.16 mg (10 mmol) of anhydrous glycolic acid (the chemical compound (28) below) and 1.51 g (10 mmol) of 1-adamantanamine (chemical compound (18)) were added to 30 ml of anhydrous pyridine and subjected to heated reflux for 3 days at 95 °C. After the reaction was finished, the reaction system was concentrated and sufficient pyridine was removed before separation and extraction using diethyl ether and hydrochloric acid with a pH of 2. After washing the diethyl ether layer, it was dried with sodium sulfate and concentrated. We tried to recrystallize it with methanol and water and obtained a white powder crystal diglycolic acid N-1-adamantylamide (the chemical compound (29) below). This chemical compound (29) was measured using NMR.

¹H-NMR: δ = 1.63 ~ 1.77 (m, 6H, H-6), 1.95 ~ 2.15 (m, 9H, H-4, H-5), 4.04 (s, 2H, H-2), 4.28 (s, 2H, H-1), 6.48 ~ 6.52 (br, 1H, H-3).

0063

[Formula 38]

/formula/

0064

Next, we introduced the side chain that we produced above to the azacrown ring. We added 174.5 mg (0.65 mmol) of the chemical compound (29) obtained above to 6 ml of an anhydrous methylene chloride solution. Stirring more, we added 0.18 ml (1.31 mmol) of triethylamine. 15 minutes later, we added 166 mg (0.65 mmol) BOP and then 15 minutes after that, we added 0.093 ml (0.33 mmol) of the kryptofix (the chemical compound (30) shown below). We stirred this in an ice bath for 2 days. After the reaction was complete, we concentrated the reaction system and ran 3 separation extractions using chloroform and hydrochloric acid with a pH of 1. We washed the chloroform layer with water, dried it using sodium sulfate and concentrated it. Next, we ran a separation and removal using HPLC for 15 minutes 45 seconds, producing 88.5 mg (recovery rate of 33.7%) of the chemical compound (31) shown below, which was like a viscous oil. We ran NMR measurements of the substance produced (31).

¹H-NMR: δ = 1.62 ~ 1.85 (m, 12H, H-13), 1.97 ~ 2.13 (m, 18H, H-11, H-12), 3.45 ~ 3.72 (m, 28H, H-1 ~ 7), 3.93 (s, 4H, H-9), 4.31 (m, 4H, H-8), 6.95 ~ 7.05 (br, 2H, H-10).

IR (cm⁻¹)

ν_{as} (C-O) = 1105.5, δ_s (NH) = 1531.7, ν_s (C = O) = 1660.7, ν_s (CH₂) = 2854.2, ν_{as} (CH₂) = 2912.7

When we performed an elemental analysis, the calculated values for the chemical compound (1) were C: 62.67%, H: 8.51%, N: 6.96%, while the actual measurements of the substance produced (32) were C: 62.7%, H: 8.6%, N: 6.9%. Thus, we were able to confirm that the product (32) was the chemical compound (1).

0065

[Formula 39]

/formula/

0066

The following is an example of synthesizing an ion-selective coordination molecule (m). The section that was to act as the side chain was prepared using the following methods. 1.16 mg (10 mmol) of an anhydrous glycolic acid (the chemical compound (28)) and 1.48 g (8 mmol) of laurylamine (the chemical compound (24)) were added to 30 ml of anhydrous pyridine and subjected to heated reflux for 3 days at 95 °C. After the reaction was finished, the reaction system was concentrated and sufficient pyridine was removed. Then, 3 separation extractions were performed using diethyl ether and hydrochloric acid with a pH of 1.2. The diethyl ether layer was washed using water, dried with sodium sulfate and then concentrated. We tried recrystallizing it with ethanol and water and produced a white crystal diglycolic acid N-dodecylamide (the chemical compound (32) shown below). We ran NMR measurements on the chemical compound (32).

¹H-NMR (eluent: CD₃OD) : δ = 0.89 ~ (t, 3H, H-14, J = 6.46), 1.20 ~ 1.60 (m, 20H, H-4 ~ H-13), 3.26 (t, 2H, H-3, J = 8.15), 4.05 (s, 2H, H-2), 4.17 (s, 2H, H-3)

0067

[Formula 40]

/formula/

0068

We introduced the side chain produced above into the azacrown ring. We added 197 mg (0.65 mmol) of the chemical compound (32) obtained above to 4.5 ml of an anhydrous methylene chloride solution and, while stirring, we added 0.18 ml (1.31 mmol) of triethylamine. After 15 minutes, we added 166 mg (0.65 mmol) of BOP and 15 minutes after that, we added 0.093 ml (0.33 mmol) of kryptofix (the chemical compound (30)). We continued stirring for 2 days in an ice bath. After the reaction was finished, we concentrated the reaction system and performed 3 separation extractions using chloroform and hydrochloric acid with a pH of 1. We washed the chloroform layer with water, dried it with sodium sulfate and then concentrated it. We ran a separation removal using HPLC and produced 30 mg (recovery rate of 10.5%) of the following chemical compound (33), which was like viscous oil. We measured the substance produced (33) using NMR.

¹H-NMR (eluent: CD₃OD) : δ = 0.88 (t, 6H, H-1), 1.15 ~ 1.40 (m, 36H, H-2 ~ 10), 1.43 ~ 1.62 (m, 4H, H-11), 3.28 (q, 4H, H-12), 3.41 ~ 3.75 (m, 28H, H-16 ~ 29), 4.06 (s, 4H, H-13), 4.34 (m, 4H, H-14), 7.50 ~ 7.65 (br, 2H, H-A15).

We performed measurements using infrared spectroscopy.

IR (cm⁻¹)

ν_{as} (C-O) = 1123.1, ν_s (C = O) = 1653.0, ν_s (CH₂) = 2851.5, ν_s (CH₂) = 2921.4

When we performed an elemental analysis, the calculated values for the chemical compound (m) were C: 63.27%, H: 10.16%, N: 6.42%, while the actual measurements of the substance produced (33) were C: 63.21%, H: 9.97%, N: 6.42%. Thus, we were able to confirm that the product (33) was the chemical compound (m).

0069

[Formula 41]

/formula/

0070

Example of Use

Figure 1 is an example of the main parts of an ion sensor using a new chemical compound of this invention as a sensing material. In this ion sensor, the electrode 1 is plated with silver chloride and either coated with polyvinyl chloride or covered with the plastic tube 2. The sensing film 3 is formed on the tip of the electrode 1. The sensing film 3 is made up of a mixture of ion-selective coordination molecules, which are the sensing material (any one of the chemical compounds (i) through (iv)), 2-nitrophenyl octyl ether (NPOE) or (di-2-ethylhexyl) sebacate (DEHS) and graphite powder. The content of each is 90 n-selective coordinating molecules: 1 ~ 5 wt %, NPOE or DEHS: 40 wt %, graphite powder: 55 ~ 59 wt %. Additionally, it is desirable to prevent a response to (penetration of) the negative ion sensing film 3 by adding 40 mol % (in relation to the ion-selective coordination molecule) of tetrachlorophenyl borate to this sensing material 3.

0071

Figure 2 shows another example of an ion sensor that uses the new chemical compound of this invention as a sensing material. The ion sensor in this example is constructed as follows. The tip of the glass or plastic tube 4 is encased in the sensing film 5, which has been gelled using polyvinyl chloride. Here the internal fluid 6, which holds the sodium ions or selectivity-neutral carrier, is stored and the electrode line 7 is immersed in the internal fluid 6. For the sensitive film 5, we dispersed one of the ion-selective coordination molecules (the chemical compounds (i) ~ (iv) and 2-nitrophenyl octyl ethyl (NPOE) or (di-2-ethylhexyl) sebacate (DEHS) or other film solvent in the polyvinyl chloride or other synthetic resin matrix. The ion-sensing substance content is to be 0.5 ~ 10 wt %. For the sensing film 5, it is desirable that 10 ~ 30 mol % of tetrachlorophenyl borate be added (in relation to the ion-sensing substance) to prevent a response (penetration) of the negative ions to the sensitive film 5. Note that a feature of this invention is that the sensing material is used in the ion sensor, so the shape and structure of the ion sensor are not restricted. All sorts of known ion sensors not shown in the figure could be used.

0072

Text Example

We tested the ion selectivity performance of the ion sensor of this invention. The selectivity of the ion sensor to ions was sought using potentiometry. That is, the ion sensor was combined with a saturated potassium chloride/silver-silver chloride reference electrode and these were immersed in the ion solution to be measured. The electromotive force generated between the electrodes was measured using a millivoltmeter. Chloride solutions such as 0.1 ~ 0.001 mol/l LiCl, NaCl, KCl, RbCl, CsCl, NH₄Cl, MgCl₂, CaCl₂, SrCl₂ and BaCl₂ solutions could be used as ion solutions to be measured. The measured electromotive force values were substituted into Nicolsky's equation below to determine the selection coefficients that would serve as the selectivity indices.

Equation 1

/equation/ Nicolsky's Equation

In the equation, R is the gaseous constant, T is the absolute temperature, F is the Faraday constant, Z_i and Z_j are the charge counts of the i ion and the j ion, a_i and a_j are the amount of ion activity, E° is the electric potential of the electrode unrelated to the amount of activity, K_{ij}^{pot} is

the selection coefficient. The measurement of the selection coefficients value depends on the use of either a mixed solution containing two types of ions (the target ions and the interfering ions) (the mixed solution method) or individual solutions (separate solution method). The ion concentration (amount of activity) will also be affected. Note that a more detailed method of measuring the coefficients of selectivity is described in JSP S59-163554.

0073

We measured the coefficients of selectivity of the lithium ions to each ion using the ion-selective coordination molecule (b) and the ion-selective coordination molecule (c) of this embodiment in the ion sensor shown in Figure 1 using the methods described above. The sensing film used in the ion sensor contained 3 wt % of the ion-selective coordination molecule (b) or (c), 0.5 wt % potassium tetrakis para chloro phenyl borate, 66.5 wt % (di-2-ethylhexyl) sebacate and 30 wt % polyvinyl chloride. The results are shown in Table 1. Note that in Table 1, the coefficients of selectivity are shown based on an interfering ion concentration of 0.1 mol/l and the mixed solution method and $\log k^{pot}_{ij}$ ($i = Li^+$) indicates the coefficients of selectivity in relation to ions other than lithium ions. Additionally, for comparison, we have included the coefficients of selectivity for the 6, 6-dibenzyl-14-crown-4 (the dibenzo-14-crown-4: chemical compound (34)) described in Citation (1) above.

[Formula 42]

/formula/

0074

Table 1

Interfering Ion j	H ⁺	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
Chemical Compound (b)	-2.8	0	-3.0	-3.8	-5.0	-4.5
Chemical Compound (c)	-2.9	0	-3.3	-3.6	-5.8	-5.5
Chemical Compound (34)	-1.6	0	-2.8	-2.9	-4.8	-4.4

0075

The results in Table 1 show that the selection coefficients of the lithium ions to the sodium ions are -3.0 and -3.3, using the mixed solution method. This means that, in the ion sensor using the chemical compound (b), the lithium ions were detected with 1000 times the sensitivity of the sodium ions and in the ion sensor using chemical compound (c), the lithium ions were detected with 2000 times the sensitivity of the sodium ions. Additionally, it is also clear that both of the chemical compounds (b) and (c) used in this embodiment were superior to the chemical compound (34) used in the comparison example. It is apparent that the ion-selective coordination molecules (b) and (c) of this invention have an extremely high degree of selectivity to lithium ions.

0076

Next, using the same sort of measuring method, we employed an ion sensor that utilized the ion-selective coordination molecules (h) and the ion-selective coordination molecules (k) to measure the selection coefficients of magnesium ions to the other ions. The sensitive material of the ion sensor contained 3 wt % ion-selective coordination molecules (h) or (k), 2 wt % potassium tetrakis para chloro phenyl borate, 68 wt % 2-nitro phenyl octyl ether and 27 wt % polyvinyl chloride. The results are shown in Table 2. Note that in Table 2, the selection

coefficients shown were obtained using the simple solution method and $\log k^{pot}_{ij}$ ($i = Mg^{2+}$) indicates the selection coefficients of the magnesium ion to other ions. For comparison, we also describe the selection coefficients of N, N''-Octamethylenebis (N'-heptyl-N'-methyl-methylmalonamide) ETH5214: chemical compound (35)), which are ion-selective coordination molecules described in Citation (2) above.

[Formula 42]

/formula/

Table 2

Interfering Ion j	H ⁺	Li ⁺	Ma ⁺	K ⁺	Mg ²⁺	Ca ²⁺
Chemical Compound (h)	+0.5	-4.0	-3.4	-1.7	0	-2.7
Chemical Compound (k)	-0.5	-3.6	-2.3	-1.0	0	-1.5
Chemical Compound (35)	+1.5	-1.2	-2.2	-2.3	0	+0.8

0078

The results in Table 2 show that the selection coefficients of the magnesium ions to calcium ions using the simple solution method were -2.7 and -1.5. The table shows that with an ion sensor using the ion-selective coordination molecules (h), it could detect magnesium ions with 500 times more sensitivity than calcium ions and when the ion-selective coordination molecules (k) were used, the sensor could detect magnesium ions with 32 times the sensitivity of calcium ions. Additionally, it is clear that this is superior to the chemical compound (35) used in the comparison example. It will be seen that when using the ion-selective coordination molecules (h) and (k) of this invention as sensing materials, an extremely high degree of selectivity to magnesium ions is obtained.

0079

The selection coefficients of calcium ions on ion sensors using the ion-selective coordination molecules (l) and (m) to each of the other ions are presented in Table 3 in the same manner. The sensitive material of the ion sensor using the ion-selective coordination molecules (l) contained 3 wt % of the ion-selective coordination molecules (l), 1.8 wt % potassium tetrakis para chloro phenyl borate, 68 wt % 2-nitro phenyl octyl ether and 27.2 wt % polyvinyl chloride. Additionally, the sensitive material of the ion sensor that used the ion-selective coordination molecules (m) contained 3 wt % of the ion-selective coordination molecules (m), 1.7 wt %, 1.7 wt % potassium tetrakis para chloro phenyl borate, 68 wt % 2-nitro phenyl octyl ether and 27.3 wt % polyvinyl chloride. In Table 3 shows the selection coefficients using the simple solution method at an interfering ion concentration of 0.1 mols/l, where $\log k^{pot}_{ij}$ (where $i = Ca^{2+}$) indicates the selection coefficients of calcium ions to the other ions. Additionally, for comparison, we have also included the selection coefficients of the ion-selective coordination molecules described in Citation (3) above, which is N, N, N', N'-Tetracycloheptyl-3-oxapentanediamide (ETH129: chemical compound (36)).

[Formula 44]

/formula/

Table 3

Interfering Ion j	H ⁺	Li ⁺	Ma ⁺	K ⁺	Mg ²⁺	Ca ²⁺
Chemical Compound (l)	-2.8	-4.8	-4.5	-4.5	-4.7	0
Chemical Compound (m)	-2.5	-4.5	-4.3	-4.3	-4.3	0
Chemical Compound (36)	-1.6	-3.3	-3.7	-4.0	-4.9	0

0081

As is clear from the results in Table 3, the selection coefficients of the calcium ions to all ions but hydrogen, Li⁺, Na⁺, K⁺ and Mg²⁺ are -4 or lower using the simple solution method. This means that calcium ions can be detected with approximately 1000 times more sensitivity than the other ions. Additionally, it is also clear that it is superior to the chemical compound (36) used in the comparison example. Thus, it is apparent that, when used as sensing materials, the ion-selective coordination molecules (l) and (m) of this invention have an extremely high degree of selectivity to calcium ions.

0082

Effect of the Invention

As described above, the ion-selective coordination molecules (i) and (ii) that are 14 crown 4 inducers and the new materials of this invention, exhibit a high degree of selectivity to lithium ions, in particular when used as a sensing material in ion sensors. Also, the ion-selective coordination molecules (iii) and the ion-selective coordination molecules (iv), which are armed azacrown inducers, are sensing materials for use in ion sensors that have a high degree of selectivity to magnesium ions and calcium ions, respectively. Ion sensors (ion electrodes) having a high degree of selectivity that are made with these molecules are extremely useful. They can be used in a wide variety of fields including industrial processes, foods and basic medical research. Additionally, because the ion sensors that utilize the ion-selective coordination molecules of this invention have such an extremely high degree of sensitivity, they will allow further miniaturization of ion sensors. By attaching a miniature ion sensor to a hypodermic needle or catheter, it would be possible to gather local data or many sensors could be put together for multifunctional uses or hybrids to be used to perform new tasks.

Brief Description of the Drawings

Figure 1 is a schematic sectional diagram showing a typical ion sensor using the ion-selective coordination molecules of this invention as a sensing material.

Figure 2 is a schematic sectional diagram showing a typical ion sensor using the ion-selective coordination molecules of this invention as a sensing material.

Description of Symbols

- 3 Sensing Film
- 5 Sensing Film

Figure 1

Figure 2